REMARKS

Claims 62-131 are pending in the application.

The amendments to the specification add no new matter. The paragraphs of Examples 1-25 have been corrected for punctuation and formatting. The amendments also provide consistency in tense. Now all of the verbs in Examples 4-25 are in the present tense, in accordance with the prophetic nature of these Examples.

Claims 64, 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 108, and 111 have been amended to perfect antecedence. These amendments add no new matter.

Claims 67, 70, 73, 76, 79, 82, 85, 88, 91, 94, 97, 100, 103, 106, 109, 112, and 115 have been amended to simplify the claim language. These amendments add no new matter.

Claims 117 and 120 have been amended to recite that a method that detects the ability of the hydroxylamine to reduce amyloid β peptide-induced neuronal cell death and a method that detect the ability of the hydroxylamine to reduce amyloid β peptide-induced locomotor impairment in rats, respectively. This amendment adds no new matter.

For convenience, the objections/rejection will be addressed in the order presented in the Office Action mailed September 22, 2004.

Information Disclosure Statement

Enclosed herewith is an Information Disclosure Statement, which includes the references cited in Applicants' response filed December 3, 2003, as well as additional references.

Rejection under 35 U.S.C. § 112, first paragraph-enablement

Claims 117 and 120 are rejected as allegedly not enabled. The Examiner argues that the claims are not enabled for detecting the ability of a primary N-hydroxylamine to protect against amyloid β peptide-induced neuronal cell death, or to protect against amyloid β peptide-induced locomotor impairment. He does, however, acknowledge that the claims are enabled for reducing neuronal cell death and locomoter impairment induced by amyloid β peptide (*see,* Office Action mailed September 22, 2004, page 4, section 8). Although Applicants

believe that this issue may be largely a matter of semantics, in order to expedite prosecution, the claims have been amended to recite that the primary N-hydroxylamine reduces amyloid β peptide-induced neuronal cell death (claim 117) and locomoter impairment (claim 120). The rejection is therefore obviated by the claim amendments.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 66, 67, 69-91, 93, 94, 101-106, and 113-115 were rejected as allegedly indefinite for lacking sufficient antecedent basis. Claim 64 has been amended to recite "substituted or unsubstituted (C1-C18) alkyl". The language in the claims at issue is therefore properly supported in claim 64. For example, the recitation of "unsubstituted (C1-C10) alkyl" in claim 67 is encompassed in the term "substituted or unsubstituted (C1-C18) alkyl" in claim 64. Claim 64 thus provides proper support.

Claims 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 111, and 114 were rejected as allegedly indefinite in the recitation of the limitation "R" in each of these claims. The claims have been amended to refer to R_1, R_2 and R_3, rather than "R".

In view of the foregoing, Applicants respectfully request withdrawal of the rejections.

Rejection under 35 U.S.C. § 103

The Examiner rejected the claims as obvious over Krishna *et al.* (*J. Med. Chem.* 41:3477-3492, 1998). The Examiner characterizes Krishna *et al.* as teaching the protective effect of secondary hydroxylamines, and screening of secondary hydroxylamines for efficacy as antioxidants. The Examiner argues that one of skill would have been motivated to employ the methods of Krishna *et al.* to evaluate other antioxidants or cytoprotective hydroxylamine compounds to protect cells from the deleterious effects due to oxidative damage. In particular, he contends that the artisan would be motivated to use primary hydroxylamines because they are less sterically hindered than the secondary N-hydroxlamines due to the absence of a secondary carbon-containing moiety, and would therefore react more readily than the secondary hydroxylamines. Applicants respectfully traverse this rejection.

As the Examiner knows, in order to establish a proper *prima facie* case of obviousness, the Examiner must establish that there is a suggestion or motivation to modify the references or to combine the reference teachings; there must be a reasonable expectation of success; and the references or combination of references must teach or suggest all of the claim limitations (*see, e.g.,* MPEP § 2142). The teachings or suggestions to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cr. 1991)). The arguments advanced by the Examiner fail to meet all of these criteria.

Krishna *et al.* studied the effect of ring size, oxidation state and redox midpoint potentials of five and six-membered secondary nitroxides. The intermediate reduced forms of Krishna's nitroxides are the corresponding five or six-membered secondary hydroxylamines (*e.g.* compounds 1b, 2b, 5b, 6b, 9b, 11b-17b, 19b, 22b, 23b, 25b-27b, 29b, 36b-38b, 40b, 42b, 48b, 52b, 53b, and 55b; p.3478, col.2, lines 31-33).

Krishna *et al* teaches the importance of "stable nitroxides" and their secondary hydroxylamine and amine precursors (Abstract, line 1; p.3477, col.2, line 24; p.p3478, col.1, lines 28 and 44; p.3480, col.2, line 25). Nitroxide free radicals depend on the presence of two tertiary carbon substituents on the nitrogen atom for stability (*see, e.g.,* Keana, "*New Aspects of Nitroxide Chemistry*," In *Spin Labeling: Theory and Applications*; Berliner, L. J. Ed.; Academic Press, 1979; Vol. 2, Chapter 3, pp 115-172, copy provided with the IDS submitted herewith). The Examiner proposes that one of skill would choose to substitute one of the two carbon moieties of the secondary hydroxylamines in Krishna *et al.* with a hydrogen. However, this would destabilize the structures. The Examiner's proposed modification thus does not logically follow from the emphasis in Krishna *et al.* on the ability of stable nitroxides to act as anti-oxidants. The Examiner provides no other evidence or reasoning as to why one of skill, upon reading the disclosure in Krishna *et al.*, would be motivated to compromise the stability of Krishna's compounds by substituting one of the stabilizing carbon moieties with a hydrogen.

Furthermore, Krishna *et al.* focuses on evaluating the effects of changes in the ring structure on antioxidant activity. Applicants' invention is based on the importance of the primary N-hydroxylamine functional group, which of course does not cyclize. In order to arrive

at Applicants' invention, a practitioner in the art would in fact have to ignore the central emphasis of Krishna *et al.* on the ring structure and realize that the ring structure is not required at all for cytoprotection. The reasoning underlying the Examiner's arguments thus appears to be based on hindsight, in view of Applicants' disclosure, not on the teachings of Krishna *et al.*, as read by one of skill in the art.

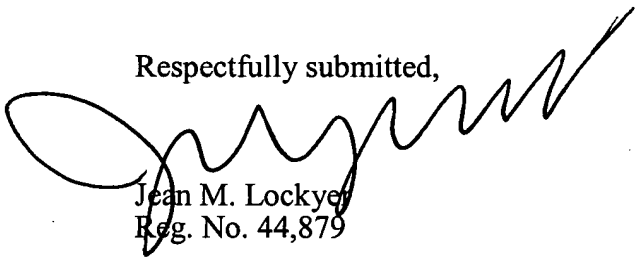
In view of the foregoing, the Examiner has not established a proper case of *prima facie* obviousness. Applicants therefore respectfully request withdrawal of this rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200..

Respectfully submitted,



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